Guidance on the use of antiviral agents for the treatment and prophylaxis of Influenza

04/04/2025

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Foreword

The influenza antiviral neuraminidase inhibitors (referred to herein as antivirals) are currently only recommended for the treatment of severe influenza and prophylaxis (prevention) of seasonal influenza for asymptomatic persons at **extremely high risk** for hospitalization (WHO) if they were to develop seasonal influenza (1).

In keeping with **WHO international guidelines** cited above, this guidance recommends that treatment should only be offered to those with severe illness (influenza/ILI) and the targeted use of antivirals for the treatment of non-severe influenza in patients at high risk of progression to severe disease **following a risk benefit analysis at the clinician's discretion**.

Antivirals may be prescribed at any time in the secondary care setting for patients with suspected or confirmed influenza. However, it is recommended that prescribing of antivirals in primary care only occurs in those with severe illness and when the Health Protection Surveillance Centre (HPSC) issues an alert that influenza viruses are circulating in the community (1).

Due to the complex nature of influenza management, clinicians with enquiries about individual patients may wish to seek specialist advice about the use of antivirals from local consultant medical microbiologists, consultants in infectious diseases and virologists. Early specialist advice is recommended for the management of all patients with severe influenza. Regional Departments of Public Health should be notified of all local influenza/acute respiratory outbreaks. Separate guidance on management of influenza outbreaks in RCF is available on the HPSC website.

As influenza management is a complex and evolving area, this guidance document may be updated during the season.

This guidance review was undertaken by a multidisciplinary subject matter expert group convened by the Winter Preparedness Lead following the updating of the Clinical Practice Guidelines for Influenza by the World Health Organization (WHO) in September 2024 (1). Please refer to Guideline Development Group Membership for membership of the group. The methodology applied to develop this guidance was based primarily on good practice guidance (GPG) recommendations.

Guideline Development Group Membership

Name	Title	Organisation
Augustine Pereira (Chair)	Director of Public Health, Winter Resilience Lead	National Health Protection Office, HSE
Anne Sheahan	Area Director of Public Health, National Specialty Director for Public Health	Department of Public Health - HSE Southwest
Cillian de Gascun	Consultant Medical Virologist and Laboratory Director	National Virus Reference Laboratory, University College Dublin
Claire Gilbourne	Health Protection Researcher	National Health Protection Office, HSE
Daniel Hare	Consultant Clinical Microbiologist and Deputy Laboratory Director	UCD National Virus Reference Laboratory
Éamonn O' Moore	Director of National Health Protection,	National Health Protection Office, HSE
Eimear Brannigan	Clinical Lead, Consultant Infectious Diseases, Antimicrobial Resistance and Infection Control Team	Office of the Chief Clinical Officer, Health Service Executive
Keith Ian Quintyne	Consultant in Public Health Medicine sí Health Protection, Lead in Evidence Based Medicine, Research & Quality Improvement	National Health Protection Office, HSE
Lois O' Connor	Consultant in Public Health Medicine, National Health Protection Office	National Health Protection Office, HSE
Louise Marron	Consultant in Public Health Medicine	HSE National Immunisation Office, HSE
Marie Philbin	AMRIC Chief Pharmacist	Office of the Chief Clinical Officer, Health Service Executive
Randal Parlour	Research and Guideline Development Unit Coordinator	National Health Protection Office, HSE
Paul Ryan	AMRIC GP Lead	Antimicrobial Resistance and Infection Control Team Office of the Chief Clinical Officer Health Service Executive
Scott Walkin	Antimicrobial Resistance & Infection Control Clinical Lead & Assistant Scheme Director	Irish College of GPs

What has changed since the last version?

Version	Date	Changes from previous version	Draft by
3.5	02/12/2024	• Align with *WHO Clinical Practice Guidelines for Influenza* September 2024 ○ Update terminology to align with WHO, complicated and non-complicated to *severe and non-severe influenza* ○ Update to align with WHO classification, *high risk of hospitalisation* and *extremely high risk of hospitalisation* ○ Use of antivirals for treatment of **severe** influenza ○ Treatment for patients with **non-severe** influenza but at *high risk of progression to severe disease* based on clinical discretion following a risk benefit analysis. ○ Treatment *for asymptomatic persons at extremely high risk for hospitalization if they were to develop seasonal influenza.*	Winter Resilience Lead RGDU, HPSC, AMRIC, NHPO
3.4	14/12/2023	• Update for 2023/2024 Winter season	RGDU, HPSC, AMRIC, Resp-Sig
3.3	25/11/2022	• Minor amendments to Appendices D and E	RGDU, HPSC & AMRIC
3.2	09/11/2022	• Inserted Appendices D and E for antiviral treatment and prophylaxis in Residential Care Facilities • Updated reference list	RGDU, HPSC & AMRIC
3.1	20/12/2021	• Added in point in the introduction regarding the co-circulation of influenza and SARS-CoV-2	HPSC
3.0	4/11/2021	• Description of zanamivir inhaled status expanded to “authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland” • Removal of peramivir (withdrawn from use in the European Union 20/11/2020) • Updated licensed indication for oseltamivir oral suspension to include treatment of those under 1 year, including full term neonates (as per EMA authorisation) • Oseltamivir licensed for post exposure prevention of Influenza in those≤ 1 year during a pandemic influenza outbreak • SmPC links updated • Change of wording in expression of dosing in all tables, for example BD changed to every 12 hours • Rename and update of Appendix B and removal of all agents without an EMA authorisation for influenza treatment/prophylaxis	AMRIC & HPSC
2.0	04/11/2020	• In the previous version it was stated that treatment with zanamivir (unlicensed available as inhaler) should be initiated within 36 hours of symptom onset. In this	AMRIC & HPSC

		updated version this advice has been amended to state that treatment with zanamivir (unlicensed available as inhaler) should be initiated within 48 hours of symptom onset for adults and 36 hours for children. • Previous recommendation that use of oseltamivir as treatment for longer than 5 days is an off-label use has been amended to state that use of oseltamivir as treatment for longer than 5 days in patients other than those who are immunocompromised is an off-label use.	

Definitions

Non severe influenza: Uncomplicated, non-severe, influenza illness is characterized by symptoms including a sudden onset of cough, headache, muscle and joint pain, severe malaise, sore throat and rhinorrhea, with or without fever. Most people recover from the fever and other symptoms within a week, without requiring medical attention. Defined as absence of any criteria of severe disease (1).

Severe influenza: Influenza virus can also cause severe illness (such as sepsis, septic shock, severe pneumonia, acute respiratory distress syndrome [ARDS], multi-organ failure, exacerbation of chronic medical conditions) or death. These conditions would normally require hospitalization and in some severe and critical cases the provision of oxygen, mechanical ventilation (invasive or non-invasive) and/ or vasopressor therapy. Patients with novel influenza A associated with high mortality, or with an unknown risk of severe disease, should be considered as "severe influenza" even if they do not otherwise fulfil the criteria (1).

WHO Classification

Patients at higher risk of hospitalisation include those with at least one major risk factor;

- aged 65 years and older
- immunocompromising conditions
- cardiovascular disease
- neurological disease
- chronic respiratory disease.

Additional risk factors include:

- malignancy
- pregnancy
- diabetes.

Patients at extremely high risk of hospitalisation are defined as:

- Age 85 years or more; or
- Any age + multiple major risk factors

This guidance should be used by clinicians in conjunction with the summary of product characteristics (SmPC) for these medicines, particularly with reference to the contraindications, interactions and adverse events.

Introduction

The evidence base for therapeutics for influenza continues to evolve with several randomized controlled trials (RCTs) recently completed and others under way (2, 3). Influenza antiviral neuraminidase inhibitors (NAI) can be used to treat patients with severe influenza or prevent influenza. Antiviral medications are an important adjunct to vaccination and infection prevention and control practices in the control of influenza. Influenza vaccination and infection prevention and control practices are of the utmost importance in the prevention of influenza and are universally preferred over the administration of chemoprophylaxis. Separate guidance of the management of influenza in RCF is available on the HPSC website.

The purpose of this updated guidance document is to assist clinicians in the care of persons with suspected or confirmed influenza virus infection. This update includes recommendations on the management of both severe and non-severe influenza and includes recommendations on the use of antiviral medications to prevent influenza virus infection in individuals exposed to the virus in the previous 48 hours.

SARS-CoV-2, the virus causing COVID-19, is a major addition to the respiratory virus threats for the population (4). The similar presentation of COVID-19 and Influenza makes the clinical diagnosis of influenza more challenging. This favours increased use of virological testing to guide case management and outbreak response. Please refer to the Guidance on testing for Acute Respiratory Infection (ARI) for further details. Coinfection of a patient with influenza and SARS-CoV-2 is possible and may be associated with increased mortality (5). A review of the literature found no data to indicate any adverse impact of initiating neuraminidase inhibitors in patients with COVID-19. COVID-19 is not a contraindication to prescribing influenza antivirals where prompt initiation for suspected or confirmed influenza is required (4).

Two antiviral medications are recommended for use in Ireland during the influenza season: oseltamivir and zanamivir (inhaled & intravenous). It should be noted that zanamivir inhaler is authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland. Both oseltamivir and zanamivir are NAI which have activity against seasonal influenza A and B.

Antiviral treatment is recommended as early as possible for any patient with suspected or confirmed severe influenza who:

1. is hospitalised
2. has severe complications or progressive illness

Antiviral treatment can also be considered in patients with non-severe influenza at high risk of progression to severe disease (see risk groups for influenza in Definitions section, P. 4 & 5 of this document) **following a risk benefit analysis at the clinician's discretion**. Ideally, treatment should be initiated early, within 48 hours of symptom onset if oseltamivir is being used and within 48 hours for adults or 36 hours for children if inhaled zanamivir is being used (6).

Clinical judgement based on the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since symptom onset is important when considering the initiation of antiviral therapy

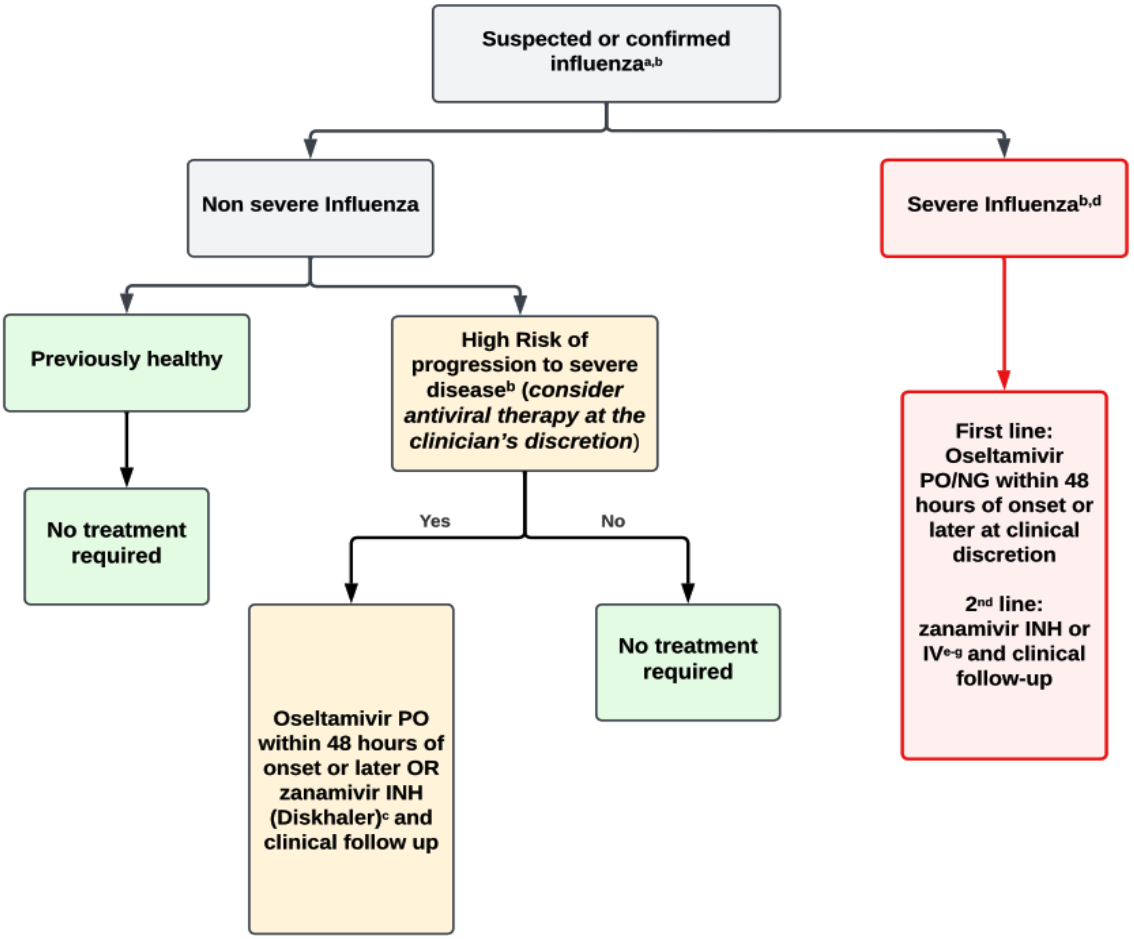
for high-risk outpatients. The greatest benefit is achieved when antiviral therapy is commenced within 36 or 48 hours of symptom onset depending on which NAI is used. However, antiviral therapy may still be beneficial in patients with severe complicated or progressive illness and in hospitalised patients when administered more than 48 hours after symptom onset (7, 8).

Empiric antiviral treatment is often necessary, and providers should not delay commencement of treatment while awaiting confirmatory diagnostic test results or if specimens are not obtained. Patients with suspected influenza should complete a full course of antiviral treatment regardless of an initial 'influenza not detected' result, unless an alternative diagnosis can be established and clinical judgement suggests that influenza is an unlikely diagnosis (6).

Section 1: Treatment of persons with suspected or confirmed influenza

Figure 1: Selection of antiviral therapy for the treatment of influenza

Please refer to the definitions provided on Page 4 when using Figure 1.



a. For treatment of suspected or confirmed oseltamivir resistant influenza, see section 1.3.2.
b. Rapid emergence of oseltamivir resistance on treatment has been described in these patients. Resistance to oseltamivir has been described in infections from influenza A(H1N1)pdm09 subtype but not in those from influenza A(H3N2) to date (personal communication with NVRL). Clinicians may consider the use of zanamivir (inhaler authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland) as first line therapy in immunosuppressed patients with suspected or confirmed influenza A(H1N1)pdm09 based on clinical judgement. In immunosuppressed patients, if no clinical improvement is seen within 5 days, test for antiviral resistance (at NVRL).
c. Inhaled zanamivir may not be an effective delivery route in some patients, including those unable to administer the inhaler and patients with severe underlying respiratory disease. It is not licensed for use in children less than five years of age. The powder preparation for the inhaler should **NEVER** be made into nebuliser solution or administered to a mechanically ventilated patient.
d. For treatment of severe influenza, see section 1.2.
e. Zanamivir is licensed for intravenous (IV) administration in Ireland and approved for reimbursement by the Health Services Executive for the following indication: - for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of a. influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see HPRA website
f. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care). Where possible, patients who have good respiratory function despite their illness and who can use the inhaler should receive inhaled zanamivir rather than IV zanamivir unless there is multiorgan failure
g. Zanamivir is available for inhalation (authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland) or as an aqueous solution for IV use.

In general, influenza A(HIN1)pdm09 is considered to be higher risk for the development of oseltamivir resistance, while influenza A(H3N2) and influenza B are considered lower risk. There are many possible subtypes that cause human infection and further advice further advice on the risk of individual subtypes can be obtained from a consultant medical microbiologist or virologist.

The risk of resistance is highest in people who are severely immunocompromised. The selection of first line drugs in severely immunocompromised individuals should take into account the influenza A subtype causing infection or, if not yet known, the dominant influenza virus type/subtype that is circulating during the influenza season. The dominant circulating influenza virus type/subtype is reported by the HPSC in Integrated Respiratory Virus bulletins during the winter period, available on **Integrated Reports - Health Protection Surveillance Centre**.

Section 1.1: Treatment of adults and children in the community/Emergency Departments with non-severe influenza

All patients should be advised of the symptoms of severe influenza and told to seek medical help should their condition worsen.

1. **Previously healthy people (excluding pregnant women**): No antiviral treatment (symptomatic treatment only)
2. **Patients with non-severe influenza and at high risk of progression to severe disease:** Oseltamivir (PO) **can be considered for an individual patient following a risk benefit analysis at the clinician's discretion** (See Table 1, section 1.3 for dosage). Treatment should be started as soon as possible, (if decision is made to treat), ideally within 48 hours of symptom onset. Treatment after 48 hours is an off-label use of oseltamivir and clinical judgement should be used**. Refer to Section 1.3.2** on **Treatment of oseltamivir resistant influenza** for suspected or confirmed oseltamivir resistant influenza in a patient who requires treatment.

Section 1.2: Treatment of adults and children with severe influenza

All patients with severe influenza should receive treatment, usually in hospital. Rapid testing for respiratory viruses including influenza virus is recommended for all patients fulfilling the clinical criteria for complicated infection. Treatment should be started as early as possible. Do not wait for laboratory confirmation of influenza virus infection.

Note:

1. Ensure that appropriate infection prevention and control precautions are applied to all patients. See HPSC website.
2. Previous influenza immunisation does not exclude influenza as a possible diagnosis.
3. The duration of therapy depends on the clinical response.
4. Test for antiviral resistance in patients who do not respond after five days of treatment (at NVRL).

The following recommendations include the use of IV zanamivir**.**

First line treatment: Oseltamivir PO or NG (see exceptions below). There is evidence that PO/NG oseltamivir is adequately absorbed in critical illness at standard doses (9).

Second line treatment: If there is a poor clinical response to first line treatment or if there is poor gastrointestinal absorption, use zanamivir. Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir. Those who cannot use a zanamivir inhaler may be considered for IV zanamivir. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care).

Zanamivir is licensed for intravenous (IV) **administration** in Ireland and approved for reimbursement by the Health Services Executive **for the following indication: -** for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see HPRA website

Exceptions

Severely immunocompromised patients

1. **First line treatment:** Oseltamivir PO or NG. Treatment should be started as soon as possible. Arrange influenza A subtype testing by the NVRL and monitor clinical condition closely.
2. Rapid emergence of oseltamivir resistance on treatment has been described in these patients and they should be monitored closely.* Resistance to oseltamivir has been described in infections from influenza A(H1N1)pdm09 but not in those from influenza A(H3N2) or influenza B to date (personal communication with NVRL). **Clinicians may consider the use of zanamivir as first line therapy in immunocompromised patients with suspected or confirmed influenza A(H1N1)pdm09 based on clinical judgement**. In immunocompromised patients, if no clinical improvement is seen within 5 days, test for antiviral resistance (at NVRL).
3. **Second line treatment:** If there is a poor clinical response to first line treatment, consider use of zanamivir and test for oseltamivir resistance. If a change in treatment is clinically indicated, it is ***not*** necessary to wait for the results of the antiviral resistance testing. Ensure that appropriate infection prevention and control precautions are applied to these patients see HPSC website.

Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir. Those who cannot use inhaled zanamivir may be considered for IV zanamivir. IV zanamivir based on clinician's judgment may be considered for patients who: (a) have multi-organ involvement, or (b) require intensive care. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care) and used in accordance with the SmPC available at HPRA website

Suspected or confirmed oseltamivir resistance (e.g. contact of known oseltamivir resistant case †)

1. Do not use oseltamivir.
2. Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir. Those who cannot use inhaled zanamivir, may be considered for IV zanamivir. IV zanamivir based on the clinician's judgement may be considered for patients who have multi-organ involvement or require intensive care in accordance with the recommendations of the SmPC available on the HPRA website.

* Oseltamivir resistance sometimes within one week of treatment initiation has been reported particularly among immunocompromised patients with influenza A(H1N1)pdm09. Infection prevention and control measures are especially important for patients who are immunocompromised to reduce the transmission of oseltamivir-resistant viruses

† Sporadic oseltamivir resistant influenza A(H1N1)pdm09 has been identified including rare episodes of limited transmission; however the public health impact has been limited to date

Section 1.3 Antiviral dosage and schedules for treatment

The recommended duration of antiviral treatment is 5 days (4, 10). However, longer treatment regimens based on clinical judgement may be necessary in severely ill hospitalised patients or patients who are immunocompromised. The optimal duration of treatment for hospitalised patients with influenza is not clear. Persistent detection of viral ribonucleic acid (RNA) and 'rebound' of previously undetectable viral RNA have been described in patients with severe influenza who completed 5- or 7-day courses of oseltamivir (4, 11).

Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (e.g. critically ill patients) and in severely immunocompromised patients. The manufacturer of oseltamivir recommends a longer treatment course of 75mg PO twice daily for 10 days for immunocompromised patients. Prolonged treatment can be associated with development of antiviral resistance, particularly in immunocompromised patients, and antiviral resistance monitoring is recommended. Use of oseltamivir as treatment for longer than 5 days in patients other than those who are immunocompromised is an off-label use.

Table 1: Antiviral treatment dosages and schedules for treatment

Treatment	Premature (less than 36 weeks post conceptual age)	0-12 months (36 weeks post conceptual age or greater)	>1-12 years: Dose according to weight below:				Adults (≥ 13 years)[a]
			10-15kg	>15-23 kg	>23-40 kg	>40kg	
Oseltamivir PO (treatment course: 5 days)[b]	1mg/kg/dose every 12 hours Unlicensed (see footnote ‡)	3mg/kg/dose every 12 hours	30mg every 12 hours	45mg every 12 hours	60mg every 12 hours	75mg every 12 hours	75mg Every 12 hours
Zanamivir (see footnote §) inhaled (treatment course: 5 days)	Not licensed for use in children aged < 5 years old. For children aged ≥ 5 years of age, Dose: 10mg (two 5mg inhalations) every 12 hours						10mg (Two 5mg inhalations) every 12 hours

[a] If a person in this age group weighs 40kg or less, it is suggested that the >23-40kg dose for those aged >1-12 years is used.

[b] Duration of treatment may be extended based on clinical judgement for patients with complicated infection or those who are severely immunocompromised

Product information for oseltamivir is available on the HPRA website

Product information for zanamivir is available on the HPRA website

‡ This is an unlicensed use of oseltamivir and is based on evidence from literature and expert opinion

§ Zanamivir is approved for the treatment of persons aged ≥5 years in Ireland.

Oseltamivir

Oseltamivir oral suspension should be used for children and adults with swallowing difficulties. It is available as a 6 mg/mL oral suspension reconstituted from powder. The SmPC contains further information on extemporaneous formulation of a suspension from the capsules if oral suspension is not available.

Zanamivir

Zanamivir is licensed for intravenous (IV) **administration** in Ireland and approved for reimbursement by the Health Services Executive **for the following indication: -** for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see the HPRA website Recommendations for when to use IV zanamivir are included in section 1.2 above.

For the use of oseltamivir and zanamivir in pregnancy and breastfeeding see Appendix A. For dosing in renal dysfunction, see Section 1.3.1.

Note on dosing for extremes of weight:

Oseltamivir: no dose adjustment is needed in obese patients (12-14).

IV zanamivir: For adult patients (and adolescents with actual body weight 50kg or greater) the dose is not weight-adjusted.

In adolescents with actual body weight less than 50kg and in children, the dose is weight-adjusted. For specific dosing information please refer to the SmPC available on the HPRA website

Section 1.3.1: Dosing in patients with renal dysfunction

The information provided here on dosing in renal impairment and renal failure is intended specifically for consideration when patients have an existing history of chronic kidney disease (CKD) and renal failure results have been previously documented for the purpose of managing CKD. As with other groups, it is essential to initiate treatment as soon as possible (4).

The choice of dose in renal failure is complicated by the different measures available to describe degree of renal impairment, as well as a lack of specific data in some circumstances. Creatinine Clearance (CrCl) is used in this document as it is a more accurate measure upon which to make dosing recommendations and is congruent with the manufacturer's prescribing information for both oseltamivir and zanamivir. The limitations for using eGFR are described in the British National Formulary ('Prescribing in renal impairment'). CrCL can be estimated in adults by utilising the Cockroft and Gault equation. Both eGFR and CrCL (using Cockcroft and Gault) assume the patient's renal function is stable. Clinical judgement will be required where renal function is unstable (i.e. in acute renal failure).

It is recognised that eGFR may be more readily available at the outset of therapy. If this is the only value available then do not delay therapy and prescribe a dose according to eGFR (substituting eGFR for the CrCL figure in Table 2). Some

patients may receive a larger oseltamivir dose as a result, but this is unlikely to be harmful as clinical experience reveals a wide margin of safety. The use of IV zanamivir is anticipated to only occur in hospitals, and as such all the data necessary to make a CrCL calculation will be available; do not use eGFR in this setting.

Table 2: Recommended oseltamivir treatment dosing in renal dysfunction (adults and those aged 13 years and over)

CrCL (ml/min)	Oseltamivir PO *Treatment*
>60mL/min*	75mg every 12 hours
31-60 mL/min*	30mg every 12 hours
11-30mL/min*	30mg every 24 hours
≤10mL/min^{++}	30mg ONCE
Haemo-dialysis (HD)*	30mg ONCE and then 30mg after every HD session
Peritoneal dialysis*	30mg ONCE
Haemo(dia)filtration^{++} 1-1.8L/hr exchange rate	30mg every 24 hours
Haemo(dia)filtration^{++} 1.9 – 3.6L/hr exchange rate	30mg every 12 hours
Haemo(dia)filtration^{++}	75mg every 12 hours

Source: Summary of Product Characteristics (SmPC) updated October 2021. (*) The recommendations for haemo(dia)filtration and established renal failure are based on expert opinion.(++) (4)

Note: It is acknowledged that some of the advice for dosing in renal impairment presented in Table 2 may differ to the renal drug database; however, the dosage information presented above is consistent with the summary of product characteristics provided by the manufacturer at the time of writing.

Section 1.3.2: Treatment of oseltamivir resistant influenza

Suspected or confirmed oseltamivir resistant influenza in a patient who requires treatment: Zanamivir (inhaler). Treatment should be started as soon as possible and ideally within 48 hours of symptom onset for adults and within 36 hours for children. These patients are likely to have severe infection.

The same criteria as for non-resistant influenza infection apply in deciding whom to treat.

1. **Management of patients for whom zanamivir is recommended by Clinician, who are unable to administer inhaled zanamivir:** Some patients who would normally receive inhaled zanamivir are unable to use it, either due to underlying severe respiratory disease or inability to effectively administer the inhaler (including children less than 5 years of age for whom zanamivir is unlicensed).
    a. Patients who are severely immunocompromised and cannot take inhaled zanamivir should receive oseltamivir PO. As they are at increased risk of developing oseltamivir resistant influenza, they should be reviewed clinically to assess response to therapy.
    b. Patients who have suspected or confirmed oseltamivir resistant infection and cannot take inhaled zanamivir should be considered for IV zanamivir. This decision will always be based on clinical judgement.
    c. Zanamivir is licensed for intravenous (IV) administration in Ireland and approved for reimbursement by the Health Services Executive for the following indication: - for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when: (a) The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or (b) Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient. Refer to the zanamivir SmPC (summary of product characteristics) for prescribing information-see HPRA website.
    d. The use of IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care).

Section 1.3.3: Management of influenza in critical care

The principles are the same as for complicated influenza.

1. The first line therapy remains PO/NG oseltamivir and there is evidence that standard dose oseltamivir PO or NG is adequately absorbed even in critical illness (9). Increasing the dosage is no longer recommended in patients who are severely ill with influenza A due to lack of evidence that it is any more effective (15, 16). Specialist advice should be sought for dosage of patients critically ill with influenza B.
2. Zanamivir should be used when there is suspected poor gastrointestinal absorption or failure to respond to oseltamivir.
3. In intensive care, zanamivir may be given intravenously based on the clinician's judgement for situations such as multi-organ failure. The use of IV zanamivir should be supervised by a consultant in intensive care medicine and used in accordance with the recommendations as per the SmPC available on the HPRA website

Section 2: Post exposure prophylaxis

Key points:

- Chemoprophylaxis (oseltamivir orally / zanamivir inhaled) may be considered for for asymptomatic persons at extremely high risk for hospitalization if they were to develop seasonal influenza who have had recent close contact with a person with influenza or influenza like illness (ILI) in the same household or residential setting when influenza viruses are circulating in the community[**].
- Chemoprophylaxis may be considered if the contact is not adequately protected by vaccination **OR** where the person has been exposed in the context of a local outbreak, regardless of vaccination status.
- Chemoprophylaxis should be commenced within 48 hours of the most recent exposure for oseltamivir and within 36 hours for zanamivir inhaled and is administered for 10 days after the most recent known exposure to a close contact known to have influenza (4).

Influenza vaccination and infection prevention and control practices are of utmost importance in the prevention of influenza and are universally preferred over the administration of chemoprophylaxis. Antiviral medications with activity against influenza viruses are an important adjunct to these measures in the control of influenza. Both are recommended for antiviral chemoprophylaxis of influenza A and B.

Post exposure prophylaxis should be reserved for asymptomatic persons at extremely high risk for hospitalization if they were to develop seasonal influenza (see P. 5 of this guidance) who have had recent close contact (see footnote ††) with a person with influenza or influenza-like illness in the same household or residential setting when influenza viruses are circulating in the community (17). Previous influenza vaccination does not preclude the use of post exposure prophylaxis, in particular where localised outbreaks occur in residential care facilities (RCF). See Appendices D-E.

As per UK National Institute of Clinical Excellence (NICE) guidance (18), prophylaxis should be issued if the contact is not adequately protected by vaccination - that is, in the situations outlined below:

- The vaccine is not well matched to the circulating strain (Refer to HPSC Integrated Respiratory Virus bulletin, available during the winter period on **Integrated Reports - Health Protection Surveillance Centre**)
- There has been fewer than 14 days between vaccination and symptom onset· **Note**: Use of antiviral medication within two weeks after LAIV administration may adversely affect the effectiveness of the vaccine. Therefore, clinical judgement on a case-by-case basis is vital.
- Use of post exposure prophylaxis may also be considered where:
- The individual has been exposed as part of a localised outbreak (such as in a residential care facility) regardless of vaccination status, as seasonal influenza vaccination may be less effective in older persons or in those who are immunocompromised (4, 18).

[**] HPSC report when influenza viruses are circulating in the community – this can be when sentinel GP influenza positivity is >10% in combination with an epidemiological assessment of all other influenza surveillance indicators.

[††] Close contact is defined as having cared for or lived with a person who has confirmed, probable or suspect influenza or having been in a setting where there is a high likelihood of contact with respiratory droplets and/or body fluids of such a person, including having talked face-to-face with them.

https://www.cdc.gov/flu/hcp/antivirals/treatment_obstetric.html?CDC_AAref_Val=https://www.cdc.gov/flu/professionals/antivirals/avrec_ob.htm

Chemoprophylaxis is not routinely considered in at-risk groups who have been vaccinated against seasonal influenza at least 14 days prior to exposure, with the above exceptions**.**

Clinical judgement should be exercised in individual cases. If a high-risk contact becomes symptomatic, consider early commencement of antiviral treatment as per this guidance if applicable. Patients receiving chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop any signs of illness suggestive of influenza.

Decisions on whether to administer antivirals for chemoprophylaxis should be made on a case-by-case basis, taking into account:

1. the exposed person's risk of developing influenza complications
2. the type and duration of contact
3. clinical judgement (6)

Generally, post exposure chemoprophylaxis should be commenced within 48 hours of the most recent exposure for oseltamivir and within 36 hours for zanamivir and is administered for 10 days after the most recent known exposure to a close contact known to have influenza. Commencement of the administration of chemoprophylaxis >48 hours for oseltamivir and >36 hours for zanamivir is an off-label use and should be based on specialist advice only.

Section 2.1: Chemoprophylaxis in specific settings/ risk groups

Residential care facilities (RCF):

Specialist advice should be sought regarding chemoprophylaxis in these situations. See specific information on the use of antivirals for treatment in the management of influenza in adult residential care facilities in Appendix C. Information on the use of antivirals for chemoprophylaxis in influenza outbreaks in adult residential care facilities including a risk assessment is outlined in Appendix D.

Pregnant and postpartum women & neonates exposed to mothers who develop seasonal influenza in the peripartum period: please refer to the following guidance here.

Section 2.2: Selection of antivirals for post exposure chemoprophylaxis

Table 3: Selection of antivirals for post-exposure chemoprophylaxis

	Exposed to influenza A or B	Exposed to suspected or confirmed oseltamivir resistant influenza
Previously healthy (excluding pregnant women)	No prophylaxis.	No prophylaxis
At risk of severe influenza (including pregnant women, but excluding severely immunocompromised patients and excluding children aged < 5 years old)	Oseltamivir PO every 24 hours for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only.	Zanamivir INH every 24 hours for 10 days if therapy can be started within 36 hours of last contact; or after 36 hours on specialist advice only.
Severely immunocompromised patients (excluding children aged < 5 years old)	Oseltamivir PO every 24 hours for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only.	Zanamivir INH every 24 hours for 10 days if therapy can be started within 36 hours of last contact: or after 36 hours on specialist advice only. If unable to administer zanamivir INH monitor closely and begin treatment promptly if ILI symptoms develop.
Children aged < 5 years in at-risk group including severely immunocompromised children	Oseltamivir PO every 24 hours for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only.	Discuss with specialist.

Section 2.3: Antiviral dosage and schedules for post exposure chemoprophylaxis

Table 4: Antiviral dosage and schedules for chemoprophylaxis

Prophylaxis	Premature (< 36 weeks post conceptual age)	0-≥12 months (36 weeks post conceptual age or greater)	>1-12 years: Dose according to weight below				Adults (≥13 years)[a]
			10-15kg	>15-23kg	>23-40kg	>40kg	
Oseltamivir PO (prophylaxis course: 10 days)	See below (see footnote ‡‡)	3 mg/kg every 24 hours[b]	30 mg every 24 hours	45 mg every 24 hours	60 mg every 24 hours	75 mg every 24 hours	75 mg every 24 hours
Zanamivir INH (prophylaxis course: 10 days)	Not licensed in children aged <5 years old Children aged ≥5 years: 10 mg (two 5mg inhalations) every 24 hours						10 mg (two 5 mg inhalations) every 24 hours

[a] If a person in this age group weighs 40 kg or less, it is suggested that the >23-40 kg dose for those aged >1-12 years is used.
[b] Only indicated in those less than 1 year of age during a pandemic influenza outbreak (SmPC)

Oseltamivir

Oseltamivir oral suspension should be used for children and adults with swallowing difficulties. It is available as a 6 mg/mL oral suspension reconstituted from powder. Its licensed indication for post exposure prevention in infants less than 1 year is only for use during a pandemic influenza outbreak. However, its use is supported by the BNF for children in this age category. The SmPC contains further information on extemporaneous formulation of a suspension from the capsules if oral suspension is not available.

Zanamivir

Inhaled zanamivir is not licensed for children less than five years of age and is unlikely to be an effective delivery route in this age group. In addition, patients with severe underlying respiratory disease may be unable to use the inhaler effectively.

Children under five years of age who are severely immunocompromised and all other severely immunocompromised patients who cannot use the zanamivir inhaler and require prophylaxis after exposure to currently circulating antiviral sensitive strains of influenza should receive oral oseltamivir with advice to seek medical attention if they become unwell (Table 3).

‡‡ Although it may be possible to provide half of the daily treatment dose for 10 days there is currently no publicly available dosing information for oseltamivir prophylaxis in pre-term infants, so it is outside the product license.

Section 2.3.1: Dosing in patients with renal dysfunction

General considerations about prescribing for renal impairment discussed in the treatment section (section 1.3.1) may also be applicable when prescribing for prophylaxis, except that the dosage of oseltamivir in Table 5 should be used (4).

Table 5: Recommended oseltamivir prophylaxis dosing in renal impairment (adults and those aged 13 years or over)

CrCL (ml/min)	Oseltamivir PO prophylaxis
>60mL/min*	75mg every 24 hours
31-60 mL/min*	30mg every 24 hours
11-30mL/min*	30mg every 48 hours
≤10mL/min++	30mg ONCE, repeated after 7 days
Haemo-dialysis (HD)*	30mg ONCE and then 30mg after every second HD session
Peritoneal dialysis*	30mg ONCE, repeated after 7 days
Haemo(dia)filtration++ 1-1.8L/hr exchange rate	30mg every 48 hours
Haemo(dia)filtration++ 1.9-3.6L/hr exchange rate	30mg every 24 hours
Haemo(dia)filtration++ >3.6L/hr exchange rate	75mg every 24 hours

Source: Summary of Product Characteristics updated October 2021. (*). The recommendations for haemo(dia)filtration and established renal failure are based on expert opinion (++) (4)

Note: It is acknowledged that some of the advice for dosing in renal impairment presented here may differ to the renal drug database; however, the dosage information presented above is consistent with the summary of product characteristics provided by the manufacturer, at the time of writing.

No difference in prophylaxis dosing for high flux and low flux intermittent haemodialysis (HD) is recommended due to a lack of published clinical data on oseltamivir carboxylate levels in high flux intermittent HD patients; this advice is expert opinion based on information on pore size, OC molecule size and likely length of HD sessions.

For dose adjustment in renal impairment in children aged less than 13 years, adjust the oseltamivir dose as per the oseltamivir chapter in the BNF for children: https://bnfc.nice.org.uk/drug/oseltamivir.html#renalImpairment

Appendix A: Use of antivirals in hepatic dysfunction, renal dysfunction, pregnancy or breastfeeding

Table 6: Use of antivirals in hepatic dysfunction or renal dysfunction

	Liver dysfunction	Renal dysfunction
Oseltamivir PO	Standard dosing	**See product information for oseltamivir available on the** HPRA website
Zanamivir INH	Standard dosing	See product information for zanamivir available on the HPRA website
Zanamivir solution IV	Standard dosing	See product information for zanamivir IV available on the HPRA website

Use in Pregnant women

Antivirals have been recommended for pregnant women due to the adverse clinical outcomes that have been observed for influenza infection in this group. Oseltamivir remains the first line option for the vast majority of pregnant women with influenza, including during seasons that are dominated by influenza A(H1N1)pdm09. For pregnant women who meet additional criteria for requiring zanamivir first line, further assessment (i.e. rapid diagnostics) and antiviral treatment should be discussed with a local infection specialist. Oseltamivir is generally well tolerated in patients with influenza, but side effects can occur. There are no data suggesting tolerability differs between pregnant and non-pregnant adults. Recent studies suggest there is no evidence of harm in pregnant women treated with oseltamivir or zanamivir (19, 20).

The Summary of Product Characteristics (SmPC) for oseltamivir states the following: "Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor feto/neonatal toxicity by oseltamivir. However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be made fully comparable, in particular whether or not they had influenza. Animal studies do not indicate reproductive toxicity."
"The use of Tamiflu [oseltamivir] may be considered during pregnancy if necessary and after considering the available safety and benefit information and the pathogenicity of the circulating influenza virus strain."

The Summary of Product Characteristics (SmPC) for zanamivir inhaler states the following: "Systemic exposure to zanamivir is low following administration by inhalation; however, there is no information on placental transfer of zanamivir in humans. There is a limited amount of data (less than 300 pregnancy outcomes) from the use of zanamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Relenza [zanamivir] during pregnancy, unless the clinical condition of the woman is such that the potential benefit to the mother significantly outweighs the possible risk to the foetus."

Use during breastfeeding

The UK Drugs in Lactation Advisory Service (UK DILAS) has published advice on the use of oseltamivir and zanamivir while breastfeeding: https://www.sps.nhs.uk/articles/oseltamivir-or-zanamivir-can-mothers-breastfeed-after-treatment-for-influenza-2/

Appendix B: Frequently asked questions

Q. When should I consider extending antiviral therapy beyond 5 days?

The recommended duration of antiviral treatment is 5 days (10). However, longer treatment regimens based on clinical judgement may be necessary in severely ill hospitalised patients or patients with immunosuppression. The optimal duration of treatment for hospitalised patients with influenza is not clear. Persistent detection of viral ribonucleic acid (RNA) and 'rebound' of previously undetectable viral RNA have been described in patients with severe influenza who completed 5- or 7-day courses of oseltamivir (11). Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (e.g. critically ill patients) and in severely immunocompromised patients. The manufacturer of oseltamivir recommends a longer treatment course for 10 days for immunocompromised patients. Prolonged treatment can be associated with development of antiviral resistance, particularly in immunocompromised patients, and antiviral resistance monitoring is recommended. Use of oseltamivir as treatment for longer than 5 days in patients other than those who are immunocompromised is an off-label use.

Q. What is meant by "poor clinical response to first line treatment"?

A poor clinical response in a patient receiving first line antiviral medication may constitute any of the following:

- No clinical improvement
- Progressive lower respiratory tract signs or symptoms
- New or progressive multi-organ dysfunction

Potential explanations for a poor clinical response include, but are not limited to, antiviral resistance. Antiviral resistance has been rare in recent influenza seasons but is most frequently observed in cases of infection with influenza A(H1N1)pdm09 as opposed to other seasonal influenza viruses. Additional risk factors for antiviral resistance include severe immunosuppression.

Absence of clinical improvement, or clinical deterioration, may also be caused by the natural progression of acute lung injury and the inflammatory response that accompanies influenza infection, or by secondary infection, e.g. bacterial co-infection. Therefore, decisions regarding the presence or absence of a "poor clinical response", and the underlying aetiology, must be made by the treating physician on a case-by-case basis, guided by these considerations.

Q. Which groups of patients are at risk of antiviral resistance?

Among patients in receipt of influenza antiviral treatment, immunocompromised individuals and young children are at increased risk of harbouring viruses that demonstrate antiviral resistance. This may be explained by prolonged duration of infection and/or higher viral burden compared to other patient groups. Rapid emergence of oseltamivir resistance (as early as 48 hours after initiation of treatment) has been described, particularly in severely immunocompromised individuals.[42]

Between July 2009 and April 2010, 285 cases of oseltamivir-resistant pandemic influenza A(H1N1)pdm09 infection were reported globally, including 45 cases in the UK. Of these UK cases, data regarding underlying medical conditions were available for 28. Of these 28 cases, 21 (75%) were immunocompromised, the most common underlying condition being leukaemia (11 of 21) (21).

Q. If zanamivir resistance is suspected, should I switch to oseltamivir?

No. Recent antiviral resistance surveillance data demonstrate that oseltamivir resistance remains more common than zanamivir resistance. Several mutations that confer resistance to zanamivir are also associated with resistance or reduced susceptibility to oseltamivir. If zanamivir resistance is suspected (e.g. as a causative factor in poor clinical response to antiviral treatment), then zanamivir treatment should be continued and urgent testing for resistance should be undertaken. Advice should be sought from local infection specialists, e.g. consultant medical virologist.

Q. What is the role of repeat sampling and laboratory testing in patients undergoing treatment with antiviral medication?

It can be challenging to assess clinical improvement in specific patient groups that may demonstrate atypical or minimal clinical signs and symptoms, e.g. immunocompromised patients, or may be unable to describe their symptoms, e.g. unconscious/ventilated patients. In such patients with confirmed influenza infection who are receiving antiviral therapy, repeat/"follow-up" sampling for detection of viral RNA by polymerase chain reaction (PCR) may be considered under the following circumstances:

- Clinical deterioration or unresolving illness despite at least 5 days of antiviral medication, potentially necessitating a prolonged duration of antiviral treatment
- Development of influenza illness while in receipt of prophylactic-dose antivirals; either test at time of symptom onset or test according to clinical deterioration

Repeat sampling is not routinely recommended in patient groups or clinical contexts beyond those described above.

When repeat testing has been performed due to suspected treatment failure, antiviral resistance testing on any positive sample should be considered, and is recommended if the patient is immunocompromised. Comparing estimated viral load in the initial and repeat samples may be helpful in assessing the antiviral effect.

If oseltamivir resistance is suspected and further treatment is required, consider switching to zanamivir without awaiting results of resistance testing. Treatment interruption should be avoided as it may promote development of antiviral resistance.

If repeat/follow-up testing yields positive results, the need for ongoing IPC measures for inpatients must be considered by healthcare workers (HCW).

In some cases repeat testing may be undertaken when considering transfer of a patient with laboratory confirmed influenza from an isolation room to an open ward/unit. In this scenario, repeat testing requests should be discussed with the testing laboratory, as an immunofluorescence assay (IFA) may provide more useful information than PCR testing. This is because PCR testing detects residual viral RNA and is likely to remain positive in patients with influenza who are no longer infectious, but IFA only detects viable virus and is likely to be negative in patients who are no longer infectious, providing support for decisions to transfer such patients to an open ward/unit.

Q. Should unvaccinated hospital-based healthcare workers (HCW) with no underlying illness be offered antiviral chemoprophylaxis?

In the hospital setting, chemoprophylaxis is only recommended for at-risk groups and should not be considered as an alternative to vaccination. The use of prophylactic antivirals in individuals who are not in risk groups as an influenza outbreak control measure in the hospital setting is not recommended. HCWs who are not in risk groups may continue

to work, using appropriate personal protective equipment (PPE), and should be advised to immediately report any signs or symptoms of illness. They should be promptly excluded from work if they develop any signs or symptoms of influenza/ILI. It is imperative that the importance of annual seasonal influenza vaccination, and non-attendance at work if unwell, is emphasised to HCWs.

Q. What is the role of previous laboratory-confirmed influenza when a person presents with a new episode of ILI in the same influenza season?

The two episodes of infection should be considered separately and treatment prescribed, if indicated, on both occasions. It is entirely possible that the first infection is with an influenza A virus and the subsequent infection is with an influenza B virus, or vice versa, or subsequent infection may be with a different A/subtype, or different circulating respiratory virus, so there would be no protective effect from the first exposure.

Q. Should antiviral medication be offered in neonates exposed to mothers with seasonal influenza?

As pregnancy confers increased risk of complicated influenza, antiviral treatment of a pregnant woman with seasonal influenza should be strongly considered, commensurate with recommendations outlined earlier in this guidance document. A particular clinical challenge arises with regard to the neonate if a pregnant woman develops laboratory confirmed seasonal influenza shortly before the onset of labour. The potential mode of transmission to the neonate in such a scenario is via direct contact with the infected respiratory secretions of the mother rather than via breastmilk.

There are limited data regarding seasonal influenza infection in neonates. The Influenza Clinical Information network (Flu-CIN) study reported severe outcomes in 9.3% of children aged less than 12 months in the UK who were hospitalised with influenza A(H1N1)pdm09 during the 2009-2010 pandemic (22).

The **Summary of Product Characteristics (SmPC)** for oseltamivir oral suspension states that the medicine can be used for post-exposure prevention of influenza in infants aged over 1 year and for post exposure prophylaxis in infants during a pandemic influenza outbreak in those less than 1 year of age. Treatment of seasonal influenza in children, including full term neonates, is however, specified in the SmPC oseltamivir for capsules and oral suspension. Zanamivir inhaler is not licensed for treatment or prophylaxis in children less than 5 years of age.

There are three potential options which may be considered by mothers and clinicians in relation to neonates born to mothers with laboratory confirmed Influenza.

1. Oseltamivir oral suspension for post-exposure prophylaxis in the neonate, which may be an unlicensed indication if used outside a pandemic influenza outbreak. As prophylaxis reduces but does not eliminate the risk of infection, infants should be closely monitored for signs and symptoms of Influenza.

2. Physical separation of the symptomatic mother and asymptomatic neonate until 5 days after symptom onset. Disadvantages would include the effect on the mother baby relationship and for the neonate not being able to benefit from breastfeeding-related transfer of immune factors and nutrients. Throughout the course of temporary separation, and if the mother is severely ill, an option is that all feedings may be provided by a healthy caregiver where possible. These considerations should be included in the discussion with the mother. Women should be encouraged to express breastmilk so that the neonate can receive the

benefits of breastmilk, and to maintain the mother's milk supply in order that breastfeeding can continue once mother and baby are reunited. Detailed advice on use of Oseltamivir during breastfeeding should be sought from the Summary of Product Characteristics (SPC) here.

3. No prophylaxis for the neonate and no separation of neonate and mother. This will require careful monitoring for symptoms of influenza, a discussion in advance with the mother about prompt antiviral treatment of the neonate, and advance arrangements for rapidly accessing oseltamivir oral suspension if required (as this is more readily available via hospital pharmacies than community pharmacies). There should also be consideration of laboratory testing of a symptomatic neonate, as per existing local arrangements.

   In both scenarios 1 and 3, which doesn't involve physical separation between mother and baby, the mother should be advised of measures to reduce risk of transmission, including respiratory hygiene and cough etiquette, use of facemasks during close contact including during breastfeeding, and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

   Decisions regarding the most appropriate course of action should be made on a case-by-case basis and must involve detailed discussion between the mother and physician regarding the relative advantages and disadvantages of each potential option. This advice does not constitute a specific endorsement of the routine use of oseltamivir oral suspension for prophylaxis in neonates, but recognises that this may occur as an off-label use in specific circumstances. Such clinical scenarios highlight the importance of seasonal influenza vaccination of pregnant women; previous research has shown that this was 71% effective in preventing influenza infection in infants aged less than 6 months in England (23, 24).

Further advice on the use of antiviral agents for the treatment and prophylaxis of Influenza can be found here.

Q. Should diagnostic sampling for influenza be performed when commencing antiviral post-exposure prophylaxis?

When a decision has been made to administer antiviral prophylaxis to immunocompromised and critically ill patients who are identified as close contacts of a confirmed case, diagnostic sampling of these contacts for influenza virus detection is recommended before or at the time of commencing antiviral prophylaxis. Please note this only pertains to the aforementioned groups of patients and is not routinely undertaken.

This is based on expert advice as symptoms and signs of influenza may be absent, minimal or atypical in these patient groups, or may be difficult to assess due to their clinical status. It is important to note that prophylactic doses of antivirals can promote antiviral resistance in patients already infected with influenza virus, especially when there is underlying immunosuppression.

While prophylaxis should not be postponed while the results of influenza testing are awaited, influenza virus testing should be expedited. If testing demonstrates that a patient in receipt of a prophylactic dose of an antiviral is actually infected with influenza virus, then prophylaxis should be stopped and treatment-dose antivirals should be commenced

immediately. Any prophylactic doses received should not be counted when determining the duration of treatment-dose antivirals.

Following the positive influenza test result, physicians and HCWs should assess the need to continue transmission based precautions beyond the recommended period of seven days on a case by case basis as it is not possible to predict duration of viral shedding for this cohort of patients. Cessation of transmission-based precautions will need to be considered locally by an infection specialist, on a case by case basis.

Q. Should the standard treatment dose of oseltamivir be doubled ("double-dosing") w**hen treating patients with severe illness caused by seasonal influenza infection?**

An increase in dosage is no longer recommended in patients with severe illness caused by influenza A virus infection, due to a lack of evidence that it is any more effective than standard dosing (16).

Although it has been previously reported that higher inhibitory concentrations of oseltamivir carboxylate are required to produce an effect on Influenza B in in-vitro tests (16, 25), there is insufficient evidence to support double-dosing in patients with Influenza B in vivo (26).

Appendix C: Antiviral treatment in Adult Residential Care Facilities (RCFs)

Treatment

Key points

- Antiviral drugs for treatment and post exposure prophylaxis of influenza are a key component in influenza outbreak control in a RCF.
- Decisions regarding treatment are made on a case-by-case basis by the attending physician, who may discuss with an ID consultant or consultant virologist/microbiologist.
- Treatment should be offered to: All residents with **severe** illness (influenza/ILI).
- Consider treatment for residents with signs/symptoms of influenza/ILI who are at high risk of progression to severe disease **following a risk benefit analysis at the clinician's discretion.**
- Empiric treatment should be commenced as soon as possible after symptom onset (within 48 hours for both oseltamivir and zanamivir), without waiting for the results of viral swabs/testing.
- Chemoprophylaxis should be offered to **asymptomatic** residents as soon as possible who are at extremely high risk for hospitalization if they were to develop seasonal influenza and who are contacts of a confirmed case.

1. Use of antiviral drugs for treatment of influenza is a key component in influenza outbreak control in a RCF as many of the residents are at high risk for severe influenza (6, 27).

2. Neuraminidase inhibitors (i.e. oseltamivir and zanamivir) have been used successfully to control outbreaks caused by susceptible strains of influenza when combined with appropriate infection prevention and control measures.

3. Treatment decisions are the responsibility of the attending physician who should consult with an infectious disease consultant or consultant virologist/microbiologist if necessary.

4. Treatment should be offered to all residents with **severe** illness.

5. Treatment should be considered in residents with non-severe influenza at high risk of progression to severe disease **following a risk benefit analysis at the clinician's discretion**.

6. Empiric antiviral treatment may be considered for any resident with suspected severe influenza without waiting for the results of viral swabs/ testing.

7. Of the neuraminidase inhibitors, oseltamivir is generally the drug of choice because of the difficulty older people have in using the inhaler device through which zanamivir is administered (28).

8. Zanamivir should be used when persons require treatment for oseltamivir-resistant strains of influenza or if oseltamivir is contraindicated. Specialist advice should be sought.

9. Oseltamivir is licensed for use in Ireland. Zanamivir inhaler is authorised for use in the EU but not marketed in Ireland; zanamivir inhaler is only available as an unlicensed product in Ireland.

At the start of the influenza season, it is recommended that each RCF has procedures in place to ensure timely access to antiviral medications (oseltamivir i.e. Tamiflu) through the normal channels/pharmacy provider in the event of an influenza outbreak.

To limit the potential transmission of an antiviral drug resistant influenza virus during outbreaks in institutions, whether in acute-care settings or other closed settings, measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons including those taking antiviral drugs for chemoprophylaxis. Where contact is unavoidable, e.g. patient care by staff, infection control measures should be strictly enforced (6, 27).
For more information on dosing and side effects of oseltamivir and zanamivir, See www.hpra.ie.

Appendix D: Antiviral chemoprophylaxis in Adult Residential Care Facilities (RCFs) including Risk Assessment for chemoprophylaxis use during an outbreak of influenza/ ILI

Post-Exposure Chemoprophylaxis

1. Chemoprophylaxis involves giving a drug to prevent infection occurring. It differs from a vaccine in that protection only lasts while the drug is being taken. Chemoprophylactic drugs are not a substitute for vaccination but can be used as adjuncts in the prevention and control of influenza (29).

2. There is a lack of evidence from recent studies to inform a single approach for antiviral prophylaxis use in RCF. The decision to give antiviral prophylaxis should be based on clinical judgement, risk assessment and the severity of the outbreak (30).

3. The decision to use antivirals for post-exposure prophylaxis will be guided by Public Health following the initial public health risk assessment (PHRA) and in conjunction with the OCT if one is convened.

4. Chemoprophylaxis is usually offered to close contactswho are asymptomatic **and at** extremely high risk for hospitalization **if they were to develop seasonal influenza**. .

5. Use of antiviral prophylaxis may be particularly important during seasons when influenza vaccine effectiveness is expected to be low due to vaccine strain mismatch although early in the influenza season this information may not be readily available. The relatively low effectiveness of influenza vaccine in the elderly population should also be taken into consideration (30).

6. Chemoprophylaxis should be prescribed by the patient's physician and persons requiring post-exposure chemoprophylaxis should be provided with the most effective antiviral medications for the particular influenza virus causing the outbreak, if known.

7. Persons needing chemoprophylaxis due to exposure to persons with laboratory confirmed influenza A or influenza B should receive oseltamivir or zanamivir. [§§]

8. The decision to use either oseltamivir or zanamivir as chemoprophylaxis should take into account the health status of the resident, the characteristics of the dominant circulating influenza viruses, preferences regarding the delivery of the drug, potential adverse effects and contraindications.

9. Zanamivir should be used when persons require chemoprophylaxis as a result of exposure to influenza virus strains that are suspected of being oseltamivir-resistant or if oseltamivir is contraindicated.

10. When chemoprophylaxis is indicated, it should be started as early as possible after contact with a case of influenza infection (ideally within 48 hours for oseltamivir and 36 hours for zanamivir). If there are concerns about high attack rates or high case fatality rates, prophylaxis may be considered more than 48 hours after contact with a

[§§] One randomised controlled study on the use of oseltamivir to prevent influenza in elderly residents in nursing homes found that it was 90% effective in preventing laboratory confirmed influenza 31. Peters PH, Jr., Gravenstein S, Norwood P, De Bock V, Van Couter A, Gibbens M, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc. 2001;49(8):1025-31.

case, or for longer durations, following a risk assessment of the situation; however, it should be noted that such use is currently unlicensed and should be based on specialist advice only (32, 33).

Residents

1. In the context of an influenza outbreak in a RCF, antiviral chemoprophylaxis may be considered for all exposed residents who are asymptomatic, regardless of their vaccination status. Even when the vaccine and circulating strains are well matched, vaccine effectiveness may be lower in the elderly due to immunosenescence*** (30).

2. The decision of whether or not to administer chemoprophylaxis after consideration of exposure risk and underlying medical conditions is a clinical decision made on a case-by-case basis and guided by Public Health advise following the initial public health risk assessment (PHRA) and in conjunction with the OCT if one is convened.

3. If a decision is made to administer chemoprophylaxis to exposed residents, chemoprophylaxis should be administered to residents on outbreak affected units/ wards only, with active daily surveillance of new cases throughout the facility.

4. In the RCF setting, post-exposure chemoprophylaxis should be commenced as soon as possible after contact with a case due to the short incubation period of influenza, and may be continued for up to 10 days after the most recent exposure to a case of influenza (30, 34)

5. When determining the timing and duration of influenza antiviral therapy for post-exposure chemoprophylaxis, factors related to compliance and potential adverse events should be considered.

6. Chemoprophylaxis should be discontinued if a causative agent other than influenza, e.g. RSV, is identified.

Staff

1. No studies have evaluated the effectiveness of giving antiviral chemoprophylaxis to health care workers during influenza outbreaks in RCF. However, studies have shown that antiviral chemoprophylaxis is effective in preventing symptomatic influenza in individuals and household contacts; therefore, staff in RCF may benefit from a protective effect offered by antiviral chemoprophylaxis (35). As the majority of HCWs are likely to be healthy adults they may benefit from the protective effect not only on a personal level, but may also protect those in their care and benefit the RCF by decreasing staff absence during the outbreak.

2. Antiviral chemoprophylaxis should be considered following a risk assessment for staff††† who provide care to residents at high risk for influenza complications, who have not had the current seasonal influenza vaccine (including those in whom influenza vaccine is contraindicated) and are in an at-risk group for influenza (including pregnant women) (32, 34)

3. Chemoprophylaxis should be prescribed by the person's own GP, Occupational Health or the RCF's attending physician/GP.

*** Immunosenescence is the impairment in immunity as a result of age-associated changes in function in a variety of cells: it is a phenomenon of decreased function, involving changes to both innate and adaptive immunity and a dysbalance between both. Any identified age-associated changes, if to be considered *senescence*, or "immune frailty", must be shown to contribute to deleterious clinical endpoints, such as decreased efficacy of vaccination in the elderly, for which there is some evidence (influenza, tuberculosis). A decreased ability to respond to pathogens in general is implied.

††† This relates to staff who do not have laboratory confirmed flu and who are not ill.

4. Unvaccinated staff in whom the vaccine is not contraindicated should receive the vaccine. However, as it may take up to two weeks for the protective effect of the vaccine to develop, chemoprophylaxis may be maintained for two weeks after receipt of the vaccine in all staff vaccinated during the outbreak.

5. Consider the possibility of antiviral resistant virus in those who become ill after starting chemoprophylaxis. Carefully exclude non-compliance. Nasopharyngeal, throat or nasal swabs from additional symptomatic people should be taken when new ILI cases arise ≥ 48 hours after commencing antiviral prophylaxis to check for the emergence of a resistant strain.

6. An emphasis on close monitoring for signs and symptoms of influenza and initiation of early antiviral treatment if indicated is an alternative to chemoprophylaxis for health care personnel.

7. All workers must be aware of the symptoms and signs of influenza and should be excluded from work if these develop.

8. Chemoprophylaxis should be discontinued if a causative agent other than influenza, e.g. RSV, is identified.

At the start of the influenza season, it is recommended that each RCF has procedures in place to ensure timely access to antiviral medications (oseltamivir i.e. Tamiflu) through the normal channels/pharmacy provider in the event of an influenza outbreak.

To limit the potential transmission of an antiviral drug resistant influenza virus during outbreaks in institutions, whether in acute-care settings or other closed settings, measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons including those taking antiviral drugs for chemoprophylaxis. Where contact is unavoidable, e.g. patient care by staff, infection control measures should be strictly enforced (6, 27, 35).

For more information on dosing and side effects of oseltamivir and zanamivir, See www.hpra.ie.

Risk assessment

Risk assessment - antiviral chemoprophylaxis use during an outbreak of influenza/ ILI in a residential care facility (RCF)

Key points

- There is a paucity of scientific evidence to inform a single approach to antiviral chemoprophylaxis use in a residential care facility (RCF). The decision to recommend antiviral chemoprophylaxis should be made on a case-by-case basis by the attending physician based on clinical judgement and risk assessment.
- In the context of an influenza outbreak in a RCF, chemoprophylaxis may be considered for:
    - **a.** all exposed residents, regardless of vaccination status (even when the influenza vaccine and circulating strains are well matched, immunosenescene[‡‡‡] may result in reduced vaccine effectiveness in the elderly compared with younger age groups)
    - **b.** RCF staff who have not received the current seasonal influenza vaccine, or received the vaccine <14 days before contact with an influenza case, and are in a high-risk group for influenza[§§§] (including pregnancy)
- If a decision is made to administer chemoprophylaxis to exposed residents, chemoprophylaxis should be administered to residents on outbreak affected units only, with active daily surveillance of new cases throughout the facility.
- Chemoprophylaxis should be started as soon as possible after contact with an influenza case (ideally within 48 hours for oseltamivir and within 36 hours for zanamivir inhaled) and continued for 10 days after the most recent exposure to an influenza case. If there are concerns about high attack rates or high case fatality rates, prophylaxis may be considered more than 36/48 hours after contact with a case, or for longer durations, following a risk assessment. During an influenza epidemic in the community the SmPC states this duration can be, up to 6 weeks (or up to 12 weeks in immunocompromised patients) for oseltamivir, and 28 days for zanamivir.
- Chemoprophylaxis should be discontinued if a causative organism other than influenza is identified.

[‡‡‡] Immunosenescence is impairment in immunity due to age-associated changes in function in a variety of cells
[§§§] http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter11.pdf

Public health risk assessment

In deciding whether or not to recommend chemoprophylaxis, the following factors should be considered:

Individual factors

Residents

- Duration of contact
- Intensity of contact[****]
- Duration of time elapsed since contact with an influenza case[††††]
- Stringency of infection prevention and control (IPC) measures in RCF and individual's ability to comply with same, e.g. cough etiquette, hand hygiene.
- Vaccination status and timing
- Vaccine match/ mismatch with causative/ dominant circulating strain
- Member of risk group for influenza, including immunosuppression
- Contraindications to antiviral chemoprophylaxis, including medication that may interact, renal function
- Ability to tolerate chemoprophylaxis – consider potential side effects
- Compliance concerns/ issues

Staff

- Duration of contact
- Intensity of contact
- Duration of time elapsed since contact with an influenza case
- Stringency of IPC measures in RCF
- Evidence of ongoing chains of transmission involving residents and staff
- Provision of care to residents at high risk for influenza complications
- Vaccination status and timing
- Vaccine match/ mismatch with causative/ dominant circulating strain
- Member of risk group for influenza, including pregnancy
- Contraindications to antiviral chemoprophylaxis, including medication that may interact, renal function
- Ability to tolerate chemoprophylaxis – consider potential side effects

Outbreak factors

- Pathogenicity of causative influenza virus subtype (if known) or dominant circulating strain – e.g. A(H3N2) is known to affect older people more severely
- Outbreak severity
- including duration, attack rate, morbidity (hospitalisation rates, ICU admission rates) and mortality

[****] e.g. sharing a room with a patient with influenza/ ILI versus resident in an unaffected unit in the same RCF

[††††] Chemoprophylaxis should be started as soon as possible after contact with an influenza case

- Distribution of cases within RCF
- Ability to implement and comply with IPC measures, e.g. isolation and spatial separation of susceptible individuals, and stringency of these measures
- Has a causative organism been identified – if causative organism other than influenza, e.g. respiratory syncytial virus (RSV), is identified, then discontinue influenza chemoprophylaxis

Examples

Chemoprophylaxis for residents:

A bed-ridden individual with chronic obstructive pulmonary disease residing in the same room as a patient with symptoms of ILI is likely to benefit from antiviral chemoprophylaxis regardless of vaccination status.

Chemoprophylaxis for staff:

A staff member who has not received the influenza vaccine and who provides care to frail, elderly residents with chronic medical conditions across a number of different units is likely to benefit from chemoprophylaxis. This staff member should also receive the seasonal influenza vaccine, but as the vaccine takes two weeks to mount a sufficient immune response, antiviral chemoprophylaxis may be considered in the interim.

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